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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/940,544	09/30/97	SADELAIN M	MSK.P-035-US

021121
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HM22/0127

EXAMINER	
HELMS,L	
ART UNIT	**PAPER NUMBER**
1642	16

DATE MAILED: 01/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/940,544	Sadelain et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *8 Nov 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) *8-20* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-7, in Paper No. 15 is acknowledged. The traversal is on the ground(s) that "In particular, most art which discloses a recombinant polynucleotide will also the discuss the protein or peptide for which it codes, because the ultimate expression of such a protein or peptide is probably why the polypeptide was made in the first place.". Applicants further traverse "the Restriction Requirement does not focuses on the specific structures of the invention, and their inter-relationship, but rather on generalized statements about polynucleotides and proteins." Further applicants traverse "while it is true that peptides could at least in theory be made by chemical synthesis, the size of the molecules argues against this as a likely approach to find in the art." Moreover, applicants traverse "It is further noted that there is substantial overlap between the classes indicated by the Examiner for the groups of claims. For example, US Patent No. 5,521,288 which claims a CD28Ig fusion protein is classified in both 536/23.4 and 530/387.3. In addition, the classification in this area does not appear so fixed that one could reasonably search a single class and consider it sufficient." This is not persuasive. Applicant has provided insufficient evidence to establish why the requirement for restriction is improper. It is unclear as to which group(s) applicants are requesting to be rejoined based on the traversal. With regards to the restriction requirements between the nucleic acids of Group I and the peptide of Group II, the Groups are distinct as recited in the Restriction Requirement. In addition, the polypeptide and nucleic acids

are district in that the polypeptide is not claimed to be made by the nucleic acid of Group I and the polypeptide could be made by chemical synthesis as the claims for Group II contain no limitation of the size of the molecule. Moreover, the protein can be made by chemically conjugating antibody domains to CD28 domains, as encompassed by the term "linked" in claim 1. As to the question of burden of search, applicant is correct that classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive, as suggested by the applicants above in the traversal, and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 8-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 15.

This application contains claims 8-20 drawn to an invention nonelected with traverse in Paper No. 15. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Claims 1-20 are pending.

Claims 1-7 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The ATCC address on page 13, line 14 needs to be updated to the current ATCC address which is 10801 University Boulevard, Manassas, VA 20110-2209.

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

c. Page 18 of the specification contains double spaces, i.e. "--" which are typically used to denote amendments. It is not clear if these are amendments to be entered or not. Replacing the "--" with other punctuation would be sufficient to obviate this objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-7 are indefinite for reciting the format fusion protein comprising A linked to B, C and D because it is not clear whether the protein comprises A, C and D, with another

polypeptide chain "B" then linked to A by disulfide bonds, etc. , for example or whether the polynucleotide encodes all of A, B, C and D. Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

b. Claim 2 is indefinite for reciting "to" for it is not clear if there are missing text and the claim had been intended to recite "binds to" or "corresponds to". Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

c. Claims 3 and 6 are indefinite for reciting the phrase "suicide gene" for the exact meaning of the phrase is not known. It is not clear how a gene can be "suicide". The gene may code for a protein that produces a "suicide" effect on a cell or host, however, it is not clear what meaning is intended. Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

d. Claims 4 and 6 are indefinite for reciting polynucleotide comprising a "region encoding a suicide gene" for the exact meaning of the phrase is not known. DNA regions typically encode mRNA or protein. DNA may comprise a gene but DNA does not encode a gene. Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

e. Claims 4 and 6 are drawn to a polynucleotide encoding a "gene".

According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as "the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons)." From the teachings of the specification, however, the "suicide gene" is not defined and appears not to be limited to the specific coding

regions, and include expression control elements that fall under the definition of a gene. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant polynucleotide illustrated in Figure 1 encoding a fusion protein comprising, in the order of amino to carboxyl terminal, the CD8α leader sequence, the polynucleotide coding for the variable region of the light chain of an anti-G_{D2} antibody, a segment of DNA coding for a peptide linker, the polynucleotide coding for the variable region of the heavy chain of an anti-G_{D2} antibody, the polynucleotide coding for the signaling domain of human CD28 receptor, the polynucleotide coding for the human CD28 transmembrane domain. Further the polynucleotide comprises a region encoding for a polynucleotide encoding thymidine kinase or bacterial cytosine deaminase outside of the region coding for the anti-G_{D2}-CD28 fusion, does not reasonably provide enablement for a recombinant polynucleotide encoding a fusion protein comprising the variable region of the light chain linked to the variable region of the heavy chain of the selected antibody, the signaling domain of the human CD28 receptor and any CD28 transmembrane domain, further comprising a region encoding for any suicide gene wherein the order of the polynucleotides coding for the fusion protein is arbitrary, and the antibody does not

bind antigen and the fusion protein, which is coded for by the "suicide gene" is not active. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims are broadly drawn to a recombinant polynucleotide encoding a fusion protein comprising the variable region of the light chain of a selected antibody linked to the variable region of the heavy chain of the selected antibody the signaling domain of the human CD28 receptor and a human CD28 transmembrane domain, further comprising a region encoding for a gene encoding any suicide gene. The claims fail to specify whether expression of DNA results in a protein which resides on the cell surface, has extracellular antibody domains and intracellular signaling domains. As written, the protein encoded by this DNA may have other membrane orientations.

c. The specification teaches a polynucleotide encoding a fusion protein comprising a single chain antibody and at least the cytoplasmic domain of the human CD28 receptor and a transmembrane domain (page 4, lines 22-25). The specification also teaches a map of the

recombinant polynucleotide encoding the single chain antibody and the portions of the CD28 receptor as Figure 1, however, the specification does not teach why the order of the map in Figure 1 is functionally important. The specification teaches "it may be advantageous to include the "suicide gene" such as a gene encoding herpes simplex virus thymidine kinase (hsv-tk) or bacterial cytosine deaminase (CDA) in the recombinant polynucleotide" (see page 6, lines 17-19). The specification teaches the single chain antibody is the anti-GD2 antibody (page 7, line 11). The specification fails to teach any arbitrary order for the map of the polynucleotides coding for the fusion protein. The claims broadly encompass any "suicide genes", however, the claims fail to provide a functional limitation for "suicide gene".

d. The claims broadly encompass a polynucleotide encoding for a fusion protein wherein the orientation or order of the DNA coding for the fusion proteins is arbitrary. The claims encompass a transmembrane domain placed arbitrarily between the variable domain of the light chain and the variable domain of the heavy chain as well as placing the transmembrane domain upstream of the antibody domain. One of skill in the art would reasonably conclude that neither of these constructions would code for a functioning antibody because the heavy chain and light chain would be on the opposite side of the plasma membrane, for example, resulting in an assembly problem.

e. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and

conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain alterations in the order of the genes coding for the fusions have the required binding function. The specification provides insufficient direction or guidance regarding how to produce fusion proteins wherein the polynucleotide is constructed in another order than that in Figure 1. Further, the specification does not teach that a functional antibody can be obtained by altering the order of the polynucleotide which could encompass insertions or deletions in the coding region of the polynucleotide as broadly claimed and still result in coding for the antibody. Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

f. Likewise, the order and placement of the "suicide gene" coding for the protein hsv-tk or CDA protein would need to be in a proper orientation with the rest of the construct in order to produce a functioning protein. The claims encompass the thymidine kinase or CDA fused to the antibody-CD28 protein, however, the polynucleotide encoding for this construct could be on 2 separate genes or 2 separate plasmids.

g. Moreover, the construct needs to be in the proper orientation for signaling function of the CD28. The signaling domains need to be in the cytoplasm for signaling. Paul (Fundamental Immunology, Raven Press Ltd., Pages 553-554, 1993) states that the cytoplasmic domain of CD28 plays a role in CD28-mediated signal transduction.

h. Further, the disclosure does not provide working examples wherein all of the steps required to practice the polynucleotide are employed. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the production of recombinant fusion proteins. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that skilled artisan is presented with a multitude of un-linked alternatives with no guidance as to which will enable use of the invention as claimed. Among these are (I) how are the proteins linked, (ii) what is the order of the fusion proteins, (iii) what orientation are the polynucleotides encoding for the protein, (iv) what cell type is used for the expression, and (v) how to maintain the activity of the antibody , signaling activity, and "suicide gene" activity.

I. Therefore, in view of the lack of guidance in the specification and in view of the unpredictability in the art as evidenced by Rudikoff et al, Panka et al, and Amit et al and the

breath of the claims and the lack of sufficient structural and functional limitations in the claims one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to.

j. Amending the claims to recite a recombinant polynucleotide encoding a fusion protein comprising (as illustrated in Figure 1), the leader sequence, the polynucleotide coding for the variable region of the light chain of an antibody, a segment of DNA coding for a peptide linker, the polynucleotide coding for the variable region of the heavy chain of an antibody, the polynucleotide coding for the signaling domain, the polynucleotide coding for the human CD28 transmembrane domain, wherein the polynucleotide comprises a region encoding for thymidine kinase or bacterial cytosine deaminase outside of the region coding for the antibody fusion or similar language fully supported by the specification as originally filed, may be sufficient to obviate this rejection.

9. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

DROP

a. The specification discloses DNA encoding thymidine kinase or bacterial cytosine deaminase (CDA). This meets the written description provisions of 35 U.S.C. 112, first paragraph. However, the claims are directed to encompass a "suicide gene", which correspond to sequences from other species, mutated sequences, allelic variants, splice variants, sequences that

have similarity or homology and so forth. According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as "the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons)." None of these "suicide genes" meet the written description provision of 35 U.S.C. 112, first paragraph.

b. Vas-Cath, Inc. v. Makurhar, 19 USPQ2d 1111, makes clear that applicant must convey with reasonably clarity to those skilled in the art, as of the filing date sought, that he or she was in possession of the invention. The invention, for the purposes of the written description inquiry whatever is now claimed (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed". See Vas-Cath Inc. v. Makurhar, page 1116).

c. With the exception of DNA encoding thymidine kinase or CDA, the skilled artisan can not envision the detailed chemical structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc v. Chugai Pharmaceutical Co. Ltd. 18 USPQ 2d 1016. One can not describe what one has not conceived. See Fiddes v. Baird 30 USPQ 2d 1481, 1483.

d. Amending the claims to recite a DNA molecule encoding for the coding region of thymidine kinase or CDA would be sufficient to obviate this rejection.

Priority

10. Acknowledgment is made of applicant's claim for priority based on the CIP application PCT/US97/04427, filed 03/20/97. It is noted, however, that there is no support or written description of the claimed limitations of the "human CD28 receptor and a transmembrane domain" recited in claim 1. Thus, the priority date granted to the claims of the instant application is 9/30/97.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending Application No. 09/142974 in view of Alvarez-Vallina et al and Sambrook et al.

a. The claims in the present and copending application are each drawn to a recombinant polynucleotide encoding a fusion protein comprising the variable region of the light chain of the anti-G_{D2} antibody linked to the variable region of the heavy chain of the anti-G_{D2} antibody further comprising a region encoding for an additional protein.

b. The claims in application 09/142974 are broader in scope that those of claims 1-7 in the instant application. Claims 1 and 2 in application 09/142974 are drawn to a recombinant single chain polynucleotide comprising a region encoding the variable region of the light and heavy chain of an anti-G_{D2} antibody and a region encoding an additional protein.

c. It would have been obvious to use the DNA encoding an additional fusion protein of human CD28 comprising the signaling domain and the transmembrane domain as well as add a DNA encoding for the thymidine kinase protein as recited in the present application because Alvarez-Vallina et al teach chimeric DNA construct containing DNA encoding a single chain antibody fusions with a DNA encoding a truncated CD28 molecule containing the human cytoplasmic signaling domain and transmembrane domain (see page 2305, 3.1) and Sambrook et al teach the thymidine kinase gene, which is expressed in most mammalian cells (Page 16.9). Sambrook et al also teach a plasmid, pTK2, which carries a fragment of the herpes simplex virus (HSV) encoding thymidine kinase (tk) (see page 16.11, Figure 16.1A).

d. One of ordinary skill in the art would have been motivated to produce the claimed invention in the instant application because Alvarez-Vallina et al teach "a scFv domain of an antibody molecule fused to the transmembrane and cytoplasmic portions of the CD28 molecule can be stably expressed on the surface of a CD28-expressing leukemic T cell line" (see page 2308, discussion). Moreover, one of ordinary skill in the art would have been motivated to produce the claimed invention because Sambrook et al teach a medium containing hypoxanthine, aminopterin, and thymidine (HAT medium) "in which only cells expressing the tk gene will grow. Thus, by using the appropriate medium it is therefore possible to select for cells expressing the tk gene".

e. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a polynucleotide encoding a fusion protein comprising a single chain anti-GD2 antibody and a signaling domain of human CD28 and human CD 28 transmembrane domain and a gene coding for thymidine kinase because Alvarez-Vallina et al teach that single chain antibody variable fragment (scFv)-CD28 molecules "can provide effective co-stimulation when binding to the antigen recognized by the scFv" (see page 2304, last lines of introduction). Also, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Sambrook et al teach a plasmid which can be used for producing a fusion gene encoding the thymidine kinase protein.

Accordingly, the claimed polynucleotide encoding a fusion protein in the copending application and the present application are obvious variants.

Therefore, the inventions as claimed are co-extensive.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Alvarez-Vallina et al (Eur. J. Immunol. (1996) 26, pp 2304-2309, Information Disclosure Statement, filed 6/3/98).

a. The claims are drawn to a recombinant polynucleotide encoding a fusion protein comprising the variable region of the light chain of selected antibody linked to the variable region of the heavy chain of the selected antibody, the signaling domain of the human CD28 receptor and a human CD28 transmembrane domain.

b. Alvarez-Vallina et al teach chimeric DNA construct containing DNA encoding a single chain antibody fusions with a DNA encoding a truncated CD28 molecule containing the human cytoplásmic signaling domain and transmembrane domain (see page 2305, 3.1). Thus, Alvarez-Vallina et al anticipates the claims.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheung et al et al (WO 97/34634, published 9/25/97, Information Disclosure Statement filed 6/3/98), and further in view of Alvarez-Villina et al (Eur. J. Immunol. (1996) 26:2304-209, Information

Disclosure Statement filed 6/3/98) and Sambrook et al (Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory, 1989).

a. The claims are drawn to a recombinant polynucleotide encoding a fusion protein comprising the variable region of the light chain linked to the variable region of the heavy chain of anti-G_{D2} antibody, signal domain of human CD28 receptor and a human transmembrane domain, further comprising a suicide gene encoding thymidine kinase.

b. Cheung et al teach a polynucleotide construct of an anti-G_{D2} antibody comprising the variable regions of a light chain linked to the variable region of the heavy chain (see abstract). Further, Cheung et al teach the antibody DNA constructs contain genes coding for fusion proteins such as streptavidin or pro-drug converting enzymes (see abstract and page 15, lines 20-26). Cheung et al fails to teach an antibody fusion protein containing the signaling domain of human CD28 receptor and a human CD28 transmembrane domain and recombinant polynucleotides encoding a fusion protein for thymidine kinase. However, these deficiencies are made up in the teachings of Alvarez-Vallina et al and Sambrook et al.

c. Alvarez-Vallina et al has been discussed supra.

d. Sambrook et al teach the thymidine kinase gene, which is expressed in most mammalian cells (Page 16.9). Sambrook et al also teach a plasmid, pTK2, which carries a fragment of the herpes simplex virus (HSV) encoding thymidine kinase (tk) (see page 16.11, Figure 16.1A).

e. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a polynucleotide encoding a fusion protein

comprising a single chain anti-GD2 antibody and a signaling domain of human CD28 and human CD 28 transmembrane domain and a gene coding for thymidine kinase.

f. One of ordinary skill in the art would have been motivated to produce a polynucleotide encoding a fusion protein comprising a single chain anti-GD2 antibody and a signaling domain of human CD28 and human CD 28 transmembrane domain and a gene coding for thymidine kinase because Cheung et al teach "gangliosides are ideal targets for monoclonal antibodies because of the high antigen density, lack of modulation, relative homogeneity in many tumors and the possibility of up regulation by cytokines" (see page 1, lines 11-13). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Alvarez-Vallina et al teach "a scFv domain of an antibody molecule fused to the transmembrane and cytoplasmic portions of the CD28 molecule can be stably expressed on the surface of a CD28-expressing leukemic T cell line" (see page 2308, discussion). Moreover, one of ordinary skill in the art would have been motivated to produce the claimed invention because Sambrook et al teach a medium containing hypoxanthine, aminopterin, and thymidine (HAT medium) "in which only cells expressing the tk gene will grow. Thus, by using the appropriate medium it is therefore possible to select for cells expressing the tk gene".

g. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a polynucleotide encoding a fusion protein comprising a single chain anti-GD2 antibody and a signaling domain of human CD28 and human CD 28 transmembrane domain and a gene coding for thymidine kinase because Alvarez-Vallina et al teach that single chain antibody variable fragment (scFv)-CD28 molecules "can provide effective co-stimulation

when binding to the antigen recognized by the scFv" (see page 2304, last lines of introduction). In addition, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Cheng et al teach "a vector encoding a ScFv is transduced into primary human lymphocytes (preferably along with a suicide gene such as HSV-TK). The transduced lymphocytes now recognize and target GD2 resulting in an immune response to the GD2 producing cells." (See page 15, lines 12-15). Also, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Sambrook et al teach a plasmid which can be used for producing a fusion gene encoding the thymidine kinase protein.

h. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art a the time the invention was made, as evidenced by the references.

18. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheung et al and further in view of Alvarez-Vallina et al.

a. The claims have been described supra.

b. Cheung et al has been discussed supra.

c. Alvarez-Vallina has been discusses supra.

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a polynucleotide encoding a fusion protein comprising a single chain anti-GD2 antibody and a signaling domain of human CD28 and human CD 28 transmembrane domain.

e. One of ordinary skill in the art would have been motivated to produce a polynucleotide encoding a fusion protein comprising a single chain anti-GD2 antibody and a signaling domain of human CD28 and human CD 28 transmembrane domain because Cheung et al teach "gangliosides are ideal targets for monoclonal antibodies because of the high antigen density, lack of modulation, relative homogeneity in many tumors and the possibility of up regulation by cytokines" (see page 1, lines 11-13). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Alvarez-Vallina et al teach "a scFv domain of an antibody molecule fused to the transmembrane and cytoplasmic portions of the CD28 molecule can be stably expressed on the surface of a CD28-expressing leukemic T cell line" (see page 2308, discussion).

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a polynucleotide encoding a fusion protein comprising a single chain anti-GD2 antibody and a signaling domain of human CD28 and human CD 28 transmembrane domain because Alvarez-Vallina et al teach that single chain antibody variable fragment (scFv)-CD28 molecules "can provide effective co-stimulation when binding to the antigen recognized by the scFv" (see page 2304, last lines of introduction). In addition, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Cheng et al teach "a vector encoding a ScFv is transduced into primary human lymphocytes (preferably along with a suicide gene such as HSV-TK). The transduced lymphocytes now recognize and target GD2 resulting in an immune response to the GD2 producing cells." (See page 15, lines 12-15).

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art a the time the invention was made, as evidenced by the references.

Conclusions

19. No Claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Art Unit:

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER